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Cyclooxygenase-2 Expression in Lymphoma in North-West of Iran

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ABSTRACT

Background: Lymphomas are a group of malignancies affecting B, T and NK cells. Cyclooxygenase-2 (COX-2) enzyme is one of the known inflammatory factors which increase during the inflammation process. Increase in COX-2 expression inhibits apoptosis and increases tumor cells invasion and angiogenesis. Increase in the COX-2 gene expression is seen in a group of cancers. Specific COX-2 inhibition also can be beneficial in some cancers through apoptosis stimulation.

Materials & Methods: In this descriptive-analytic study, the degree of COX-2 expression was evaluated in patients with non-Hodgkin lymphoma. The following variables were used in this study: gender, age, lymphoma type, the stage of disease, the degree of disease, the existence of B symptom, extranodal involvement, response to treatment, death and LDH levels. Paraffin-embedded tissue blocks from 153 cases of non-Hodgkin' and Hodgkin' lymphoma were selected for immunohistochemical staining of COX-2 expression.

Results: COX-2 level was reported positive in 4 (4.7%) patients with non-Hodgkin's lymphoma and 4 (5.7%) with Hodgkin's lymphoma. Fifteen patients experienced relapses and 9 died during the median follow-up of 7 years. There was no significant relationship between quantitative and qualitative variables and COX-2 expression. Also, there was no relationship between COX-2 and type of lymphoma (P=0.476).

Conclusion: According to our results, no relationship between COX-2 expression and type of lymphoma was found. We recommend more patient involvement to assess COX-2 expression. Apparently, it seems that the patient's race (Azari) may have an impact on the results of this study.

KEY WORDS: COX-2, Non-Hodgkin lymphoma, Hodgkin lymphoma

INTRODUCTION

Lymphomas are a group of malignancies in B, T and NK cells.[1] Chronic inflammation can be associated with cancer emergence.[2] Rudolf Virchow established the view that cancers arise at sites of chronic inflammation. This enzyme increases in the inflammations.[3]

Inflammation is one of the important factors in the cancer phenomenon.[2] COX-2 plays an important role in the tumor growth and malignant cell proliferation which is followed by an increase in angiogenesis, invasion and metastasis. There is a close relationship between COX-2 and EGFR.[4] There are two known COX types including COX-1 and COX-2. COX-1 is produced in many different situations, whereas COX-2 is produced in inflammation and cancer. COX-2 mRNA is not seen in the tissues normally, but it can increase following response to inflammation or mitogenic stimuli such as growth factor cytokines, oncogenes and several chemical factors. Increase in COX-2 expression inhibits apoptosis and increases tumor cell invasion and angiogenesis. Stimulation for activating COX-2 gene may have an import role in the emergence of cancer.[2-5] The increase in COX-2 expression can be seen in a group of cancers including pancreas, stomach, prostate, lung, colorectal, head and neck, breast and bladder. Specific inhibition of COX-2 can also be useful in some cancers by apoptosis stimulation.[2-5]

The aim of this study is to evaluate COX-2 expression degree in the patients with lymphoma. Considering the fatality and malignancy of lymphoma disease, COX-2 expression can be used as a prognostic factor; NSAIDs targeting COX-2 inhibition and increasing apoptosis and anti-angiogenesis activities can be used.

MATERIALS AND METHODS

This descriptive-analytic study was conducted in the Hematology and Oncology Clinic of Shahid Ghazi-Tabatabaei Medical Educational System, Tabriz from 2004-2010. Patients with lymphoma who had pathology reports of Hodgkin's and non-Hodgkin's lymphoma were selected. The patients were considered to study the following variables: gender, age, lymphoma type, stage of the disease (Ann Arbor Staging System), the grade of the disease (WHO classification), existence of B symptom, extranodal involvement, response to treatment, death and LDH levels. Immunohistochemistry approach was used to evaluate COX-2 expression. Informed consents were obtained from all patients. The immunohistochemistry tests were performed by the project approved in the Hemetology-Oncology research Center, affiliated with Tabriz University of Medical Sciences.

Immunohistochemistry Method

Samples were cut at 3-micrometer thickness of formalin. Fixed paraffin-embedded tissue samples were deparaffinized, rehydrated through a series of graded alcohols and blinked for endogenous peroxidase (3% H_2O_2) and avidin/biotin. Antigen retrieval was carried out in a microwave oven with peroxidase blocking reagent for 5 min. Primary monoclonal antibody for COX-2 (1/600 dilution-DAKO) was applied to the section. After washing, they were incubated for 20 min with biotinylated horse anti mouse IgG immunoglobulin (DAKO) and for 30min with strept avidin peroxidase reagent. The sections were counterstained with mayer's hematoxylin and then cover slipped. Next, 3 cellular sections were selected and evaluated, using a x20 magnification lens and degree of positivity for COX-2 in tumoral cells was reported. Quality control was performed by using positive colon cancer samples.

SPSS 13 software, Chi-square, T-test, Mann-Whitney Test, Fisher's exact test were used for statistical analyses. $P<0.005$ was considered significant.

RESULTS

In this study, 153 patients with lymphoma were included. There were 105 (68.6%) males and 48 (31.4%) females, with a median age of 40±17 years. 71 (46.4%) had B symptoms. 53 patients had stage I, 52 stage II, 41 stage III and 7 stage IV disease. 24 patients (15.7%) had extranodal lymphoma. In non-Hodgkin lymphoma, based on the histology, 21patients (24.6%) were indolent, 55 (64.7%) aggressive and 9 (10.6%) very aggressive. LDH level were 151-1237 (414±294). COX-2 level was reported positive in 4 patients with non-Hodgkin' lymphoma and 4 patients with Hodgkin' lymphoma. Fifteen patients experienced relapses and 9 died during the median follow-up of 7 years. There was no significant relationship between quantitative and qualitative variables and COX-2 expression. Also, there was no relationship between COX-2 and type of lymphoma ($P=0.476$).

DISCUSSION

Inflammation is one of the important factors in the cancer phenomenon.[2] COX-2 plays an important role in the tumor growth, malignant cell proliferation followed by increase in angiogenesis, invasion and metastasis. There is a close relationship between COX-2 and EGFR.[5] In arachidonic acid cycle, cyclooxygenase COX-2 plays an important role in the production of prostaglandins.

A number of studies on lymphoma are relatively limited, as compared with solid tumors. In the study of Li et al., COX-2 expression degree was significantly higher in the patients with lymphoma compared to the normal tissues.[8] The results of a cohort study conducted by Paydas S et al., on the patients with non-Hodgkin's lymphoma to compare COX-2 expression degree showed that 56% of patients possessed COX-2 and there was no significant difference regarding COX-2 expression between different clinical types.[5] In our study, 8 of 145 patients with lymphoma were COX-2 positive.

In a study carried out by Hazar B, there was no significant difference in the mean age of the lymphoma patients with positive / negative COX-2 (p=0.660).[4] In the current study, no significant difference was observed between lymphoma patients with positive / negative COX-2 (p=0.483).

In the study of Li B et al., the degree of positive COX-2 expression was significantly higher in the relapsed NHL.[9] In our study, 15 patients with negative COX-2 experienced relapse. In the study of Sugita Y, COX-2 was reported positive in 20 of 22 patients with nervous system lymphoma.[10]

In the study of Mohammad et al., and Wun T et al., COX-2 expression was significantly higher in the malignant lymphoid tissues compared to the normal tissues.[11-12] In a study carried out by Thum MJ, it has been confirmed that the COX-2 expression increases in the malignant lymphoid tissues significantly, but usage of NSAIDs in treating malignant tumors is not yet confirmed.[13] According to our results, there was no relationship between cox-2 expression and type of lymphoma. We emphasize that more patients are required for assessment of COX-2 expression. On the other hand, as the majority of study participants had Azeri background, the results of the study were more likely to be affected by this ethnic group.

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